Cell biology

Origins of the cytoskeleton

from Carl M. Cohen

A REPORT by Catherine Woods and Elias Lazarides on page 85 of this issue[1] shows that our understanding of membrane skeletal biogenesis shares at least one characteristic with the cells in which it has most recently been studied — both are embryonic. Lazarides and co-workers have recently provided us with fascinating insights into membrane skeletal biogenesis in chick embryo erythroid cells. Although these cells are nucleated, they nonetheless contain a membrane skeleton composed of the protein complex spectrin–actin–band 4.1 as well as the spectrin-binding protein ankyrin (goblin) which links spectrin to the integral membrane protein band 3. Lazarides' group has interpreted their observations in terms of a 'receptor-driven' membrane skeletal assembly, that is, that the amount of band 3 (the 'ultimate' membrane skeletal receptor) limits the amount of newly synthesized ankyrin that gets incorporated into the skeleton. Ankyrin is then thought to limit the amount of spectrin β chain (containing the ankyrin-binding site) which in turn limits spectrin α-chain incorporation[2]. According to this scheme, spectrin chains that are not incorporated into the skeleton as α/β heterodimers, α_2/β_2 heterotetramers or higher hetero-oligomers are degraded[3,4].

A major question raised by this model is how the unassembled chains are targeted for destruction. Woods and Lazarides' new work[1] suggests that α and β chains not incorporated into the skeleton pass their brief existence as homo-oligomers, either α_2 or β_4. These oligomers are largely incapable of forming stable functional associations within the membrane skeleton and the cytosol, and are somehow marked for destruction.

The possible existence of spectrin homo-oligomers runs counter to a small body of literature suggesting that such complexes do not form, or are rare, in solutions of purified α or β chains[5–8]. But these studies were done on mammalian erythrocyte or brain spectrins, and there may be important differences between chicken and mammalian spectrins. Although chicken non-erythroid and human erythroid spectrin chains have much in common, these two forms are probably the most widely divergent among the spectrin-chain family[9–11]. (Because chickens apparently possess only a single spectrin gene, the same must hold for chicken erythroid spectrin.) More to the point, recent unpublished studies by M. Mooseker, J. Coleman and J. Morrow at Yale University show that purified chicken erythroid β-spectrin chains have a remarkable propensity to self-aggregate. This is apparently true of fodrin chains as well[12]. Taken together, these studies suggest that for most spectrins, self-oligomerization of spectrin chains, particularly the β chain, may be the rule rather than the exception.

Intriguingly, the chains making up homo-oligomers in the chick cytosol seem to be perfectly capable of forming heterodimers if the homo-oligomers are first denatured and then mixed with their partners under appropriate renaturing conditions. Thus, there is nothing inherently different about those chains that end up as homo-oligomers. What, then determines the proportion of spectrin chains that end up as heterodimers? Is the proportion regulated by membrane-bound ankyrin? If not, what happens to the heterodimers that are synthesized in excess of ankyrin? Woods and Lazarides find no evidence for unassembled heterodimers in the cytosol of chick erythroid cells after translation *in vivo*. Are unassembled heterodimers also somehow targeted for destruction?

It seems likely that heterodimerization would take place in the cytosol during or soon after synthesis in order for the chains to be protected from self-oligomerization. In fact, the proposition that the α/β heterodimer (or α_2/β_2 heterotetramer) may form before its incorporation in the skeleton makes sense in the context of the known functional capabilities of spectrin chains. Several groups have shown that the high affinity association of spectrin in the spectrin–actin–band 4.1 complex requires an α/β heterodimer (or α_2/β_4 heterotetramer) even though isolated α and β chains bind to band 4.1 quite well[5,8]. Even fodrin, which can apparently bind to actin filaments without the need for band 4.1, must be heterodimeric for the association to occur[7]. Thus, it is more appealing to envision a fully competent heterodimer or heterotetramer forming a stable link in the nascent membrane skeleton than a single β chain arriving and waiting for its α mate.

If the homo-oligomer degradation route is operative in mammalian cells it may be less stringent, but the same principles may still apply. For example, in mice with any one of several genetic defects at the *sph* locus there is no α spectrin synthesized, whereas β spectrin is synthesized at a nearly normal rate. Almost normal amounts of β spectrin are bound to the reticulocyte membrane skeleton, and about 20 per cent of normal

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